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SCULLY SCOTT MURPHY & PRESSER, PC
400 GARDEN CITY PLAZA
SUITE 300
GARDEN CITY, NY 11530

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NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,484	CONTRERAS ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 35-89* is/are pending in the application.

4a) Of the above claim(s) *41-46,52,53,58,59,64-68 and 73-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,35-40,47-51,54-57,60-63 and 69-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 35-89 are pending in the present application.

Applicant's election with traverse of Group I in the reply filed on 8/9/06 is acknowledged. Applicants further elected the following species: (a) alpha-1,2-mannosidase derived from *Trichoderma reesei*; (b) AOX I promoter; (c) a genetically engineered methylotrophic yeast containing a combination of vectors of claims 35 and 47; (d) a method requiring transforming the methylotrophic yeast with a combination of vectors of claims 35 and 47; and (e) a kit containing a combination of vectors of claims 35 and 47.

The traversal is on the ground(s) that: (a) The separated Groups of Inventions are not independent and distinct. Specifically, Applicants argue that Groups I and II are different aspects of a single invention, while the methods of Groups I, III-IV employ one single concept, are related to each other even though they employ different reagents and comprise different steps; (b) It is in the public interest to permit applicants to claim several aspects of their invention together in one application; (c) Reliance on the supposed classification of the groups of claims does not establish independence or distinctness, and the classification system is also an unreliable and poor basis for requiring restriction between clams to the various aspects of applicants' unitary invention; and (d) The continued increase of official fees, the regulatory changes as a consequence of the GATT, and the potential limitation of an applicant's financial resources, a practice which arbitrarily imposes restriction requirements may become prohibitive and thereby contravene the constitutional purpose to promote and

encourage the progress of science and the useful arts. These not found persuasive for the following reasons.

Firstly, with respect to Applicants' interpretation of 35 U.S.C. § 121 that both independence and distinctness be present for restriction between two inventions to be proper, the law has long been established that independent inventions may be properly divided if they are in fact "distinct" inventions. See M.P.E.P. 802.01. The Courts have interpreted the statute **to mean "or" instead of "and"** in 35 U.S.C. § 121. The various distinct species of a vector (composed of nucleotide residues) in Group I are chemically and structurally distinct from a glycoprotein (made up of amino acid residues and a carbohydrate) of Group II, and that the glycoprotein of Group II can be made by another and materially different process from the method of Group I, such as it is being made synthetically or in cultured human recombinant cells. In addition, the distinctness among the methods of Groups I, III-IV were already set forth in details in the Office action mailed on 7/5/06 (pages 3-4).

Secondly, Inventions of Groups I-IV are four separate distinct inventions and not different aspects of a single invention. Therefore, it would be unduly burdensome for the examiner to search and/or consider the patentability for all of the four separate distinct inventions in a single application.

Thirdly, the Office action mailed on 7/5/06 did not establish distinctness of Inventions in Groups I-IV based on classification (see page 3 and first two paragraphs on page 4). Applicants misinterpreted the Office action (please reread the Office action in its entirety). Because of separate search requirements in both patent and non-patent

literature databases for searching the features characterized in each distinct invention, it would be unduly burdensome for the examiner to search and/or consider the patentability of all four inventions in a single patent application.

Fourthly, with respect to the issues of increased official fees, regulatory changes as a consequence of the GATT, potential limitation of an applicant's financial resources, these issues are irrelevant because they are not criteria used for restriction requirement under 35 U.S.C. 121.

The requirement is still deemed proper and is therefore made FINAL.

Claims 41-46, 52-53, 58-59, 64-68 and 73-89 are withdrawn from further consideration because they are directed to non-elected species and non-elected inventions.

Claims 1, 35-40, 47-51, 54-57, 60-63 and 69-72 are examined on the merits herein with the aforementioned elected species.

Information Disclosure Statement

The Japanese patent 8-336387 (12/24/1996) has only partially considered by the Examiner because only the abstract in English has been provided.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see pages 40, line 19; page 44, line 14 for

examples). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Sequence Compliance

The disclosure is objected to because throughout the specification, the peptide sequence HDEL has not been identified with its proper SEQ ID NO. 1 (e.g., see at least page 4, lines 4 and 17, for examples). The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. It should be noted that for any nucleotide sequence longer than 9 nucleic acid residues or any peptide sequence 4 amino acid residues or longer, a SEQ ID NO must be assigned to each nucleotide or peptide sequence every time the sequence appears. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required. Failure to do so will result in a Non-Compliant Response.

Claim Objections

Claim 1 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 35. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is

proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-48, 50, 54, 56, 60, 62 and 69-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed " Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The instant claims are drawn to a vector for disrupting the OCH1 gene in any methylotrophic yeast, a genetically engineered strain of any methylotrophic yeast in which said strain is transformed with the same vector, methods of reducing

glycosylation on proteins or heterologous glycoproteins produced by the same genetically engineered methylotrophic yeast, and a kit comprising the same vector and methylotrophic yeast strain.

The instant specification fails to provide sufficient written description for a representative number of OCH1 gene derived from a broad genus of methylotrophic yeasts, including *Candida, Hansenuala, Torulopsis and Pichia* to be used in a vector, a kit, methods for making and using genetically methylotrophic yeasts as claimed. At the effective filing date of the present application, apart from the OCH1 gene obtained from the methylotrophic *Pichia* yeast strain (Japanese Patent Application No. 07145005), little is known about the existence and/or structures of OCH1 genes derived from other genera of methylotrophic yeasts such as *Candida, Hansenuala* and *Torulopsis.* There is no indication in the prior art on the degree of relatedness or divergence of the *Pichia pastoris* Och1 gene with Och1 genes derived from *Candida, Hansenuala* and *Torulopsis genera* of methylotrophic yeast.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure

of a representative number of species for a broad genus of a vector comprising the OCH1 gene from a broad genus of methylotrophic yeast, including *Candida, Hansenuala, Torulopsis and Pichia*, to make a genetically engineered strain of a methylotrophic yeast in which the OCH1 gene is disrupted, kits and methods of uses as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 35-38, 40, 48-49, 54-55, 60-61 and 69-71 are rejected under 35 U.S.C. 102(b) as being anticipated by Martinet et al. (Biotechnology Letters 20:1171-1177, 1998; IDS) as evidenced by the pPICZB vector diagram (Invitrogen Catalog, 1998; IDS).

Martinet et al. teaches the preparation of plasmids for expression of *T. reesei* α-1,2-mannosidase or a chimeric *S. cerevisiae/ T. reesei* α-1,2-mannosidase (a fusion of the catalytic domain of *T. reesei* α-1,2-mannosidase to the ER retention signal of *S. cerevisiae* MNS1) in *Pichia pastoris* strains GSIV-HAs and GSIVNAf1s derived from the parental strain GS115 (see Materials and Methods, particularly sections "Strains and culture conditions" and "Construction of plasmids for expression of *T. reesei* α-1,2-mannosidase in *P. patoris*"). Martinet et al. further teaches that in all expression plasmids are derived from the pPICZB vector, and the *T. reesei* α-1,2-mannosidase gene was under transcriptional control of the AOX1 promoter (page 1172, col. 2, first full paragraph). The pPICZB plasmid obtained from Invitrogen contains polyhistine tag for rapid purification and detection as well as a termination sequence from the AOX1 gene (AOX1 TT) as evidenced by the pPICZB vector diagram. Martinet et al. also discloses that co-expression of heterologous *T. reesei* α-1,2-mannosidase in GSIVNAf1s resulting in partial trimming of the large influenza neuramidase (NA) N-glycans (>Man14GlcNac2) (see section "In vivo trimming of N-glycans by heterologous *T. reesei* α-1,2-mannosidase", and Figures 2A, 3). The co-expression of the chimeric MNS1/*T. reesei* α-1,2-mannosidase in GSIV-HAs resulted in the formation of both trimmed and

hyperglycosylation glycan products of hemagglutinin (HA) (see page 1175, col. 2 and Fig. 4).

With respect to claims 69-71 drawn to a kit comprising at least one of the vectors of claims 35 and 41, and the same kit further comprising a methylotrophic yeast strain, please note that articles (e.g., a cultured flask or a vial) containing plasmids for expression of *T. reesei* α-1,2-mannosidase and/or *Pichia pastoris* strains GSIV-HAs and GSIVNAf1s derived from the parental strain GS115 which are transformed with the same plasmids taught by Martinet et al. would constitute such kits.

Therefore, the teachings of Martinet et al meet all the limitations of the claims as written. Accordingly, the reference anticipates the instant claims.

Claims 1, 35-40 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Chiba et al. (J. Biol. Chem. 41:26298-26304, 1998; IDS) as evidenced by Inoue et al. (Biochim. Biophys. Acta 1253:141-145, 1995; IDS).

Chiba et al. teaches the preparation of an expression vector encoding HDEL-tagged *Aspergillus* α-1,2-mannosidase for expression in various *Saccharomyces cerevisiae* strains, named pGAMH1 plasmid (see abstract and the section "DNA constructs"). The pGAMH1 plasmid contains GAP promoter (the promoter is also functional in a methylotrophic yeast) and PGK terminator because pGAMH1 is derived from pGAM1 as evidenced from the teachings of Inoue et al. (see Fig. 3). Chiba et al. further teaches that carboxypeptidase Y produced in the YS132-8B yeasts having disrupted OCH1, MNN1 and MNN4 genes and harboring pGAMH1 plasmid has trimmed

sugar chains up to Man5GlcNAc2, instead of carboxypeptidase Y containing high mannose type sugar chains in wild type *Saccharomyces cerevisiae* (see Fig. 1, and page 26302, col. 1, first full paragraph). Additionally, Chiba et al. discloses that the Man5GlcNAc2-oligosaccharide is the intermediate for the production of hybrid-type and complex-type sugar chains, the latter of which is better suited and more effective for the production of human therapeutics, and that the *Δoch1 mnn1* double mutant yeasts are useful for the production of recombinant therapeutic glycoproteins without any antigenicity toward humans due to the accumulation of a single oligosaccharide moiety Man8GlcNAc2 in the double mutant instead of the highly antigenic mature mannan glycans formed in wild-type yeast cells (see page 26298).

With respect to claim 69 drawn to a kit comprising at least one of the vectors of claims 35 and 41, please note that articles (e.g., a cultured flask or a vial) containing an expression vector encoding HDEL-tagged *Aspergillus* α-1,2-mannosidase taught by Chiba et al. would constitute such a kit.

Therefore, the teachings of Chiba et al meet all the limitations of the claims as written. Accordingly, the reference anticipates the instant claims.

Claims 47-49, 54-57, 60-61 and 69-71 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 8-336387 (IDS).

JP 8-336387 already teaches the preparation of a vector construct comprising a portion of *Pichia* OCH1 gene and a selectable marker gene for disruption of the genomic OCH1 in a *Pichia* yeast strain, including the GTS 115 (NRRL Y-15851) strain

for inhibiting the elongation of sugar chains on glycoproteins for production of a glycoprotein having a sugar chain identical or similar to that of a medically useful biologically active protein (see at least the abstract in English, Fig. 9 on page 635 as well as col. 15, paragraph 0033). It is further noted that articles (e.g., a cultured flask or a vial) containing a vector construct comprising a portion of *Pichia* OCH1 gene and a selectable marker gene for disruption of the genomic OCH1 in a *Pichia* yeast strain and/or the *Pichia* yeast strain in the invention disclosed in JP 8-336387 would constitute such a kit.

Accordingly, the teachings of JP 8-336387 meet every limitation of the instant claims. Therefore, the reference anticipates the instant claims.

Claims 1, 35-39, 47-51, 54-57, 60-63 and 69-72 are rejected under 35 U.S.C. 102(e) as being anticipated by Gerngross (US 2002/0137134; IDS) as evidenced by JP 8-336387 (IDS).

Gerngross discloses methods and compositions by which fungi or other eukaryotic microorganisms including *Pichia pastoris, Hansenula polymorpha, Candida albicans* can be genetically modified to produce glycosylated proteins having patterns of glycosylation similar to glycoproteins produced by animal cells, particularly human cells, which are useful as human or animal therapeutic agents such as erythropoietin, cytokines, coagulation factors (See Summary of Invention, pages 4-5; page 6, paragraph 0056). Specifically, Gerngross teaches the microorganism is engineered to express an exogenous α-1,2-mannosidase enzyme (including α-1,2-mannosidase from

Trichoderma reesei, paragraph 0036) having an optimal pH between 5.1 and 8.0, and that the enzyme is targeted the endoplasmic reticulum (ER) or Golgi apparatus of the host organism, where it trims N-glycans such as Man8GlcNAc2 to yield Man5GlcNAc2 which is a substrate for further glycosylation reactions that produce a finished N-glycan that is similar or identical to that formed in mammals and it is not a substrate for hypermannosylation reactions that occur *in vivo* in yeast or other microorganisms (page 5, paragraph 0042). Gerngross also teaches that ER or Golgi apparatus targeting sequences are well known in the art such as HDEL or KDEL (page 10, paragraphs 0087 and 0088 including Table 5). Gerngross specifically teaches that the eukaryotic strains which do not express one or more enzymes involved in the production of high mannose structures are used, and that these strains can be engineered in conjunction with the introduction of an exogenous α-1,2-mannosidase enzyme (page 7, paragraphs 0064-0067), and one of the many such mutants already described in yeasts including a hypermannosylation-minus (OCH1) mutant in *Pichia pastoris* described in Japanese Patent Application Public No. 8-336387 (page 5, paragraph 0048, and page 4, paragraph 0035). JP 8-336387 already teaches the preparation of a vector construct comprising a portion of *Pichia* OCH1 gene and a selectable marker gene for disruption of the genomic OCH1 in a *Pichia* yeast strain, including the GTS 115 (NRRL Y-15851) strain for inhibiting the elongation of sugar chains on glycoproteins (see abstract in English, Fig. 9 on page 635 as well as col. 15, paragraph 0033). It is further noted that articles (e.g., a cultured flask or a vial) containing vectors for expression of exogenous α-1,2-mannosidase enzyme and for disruption of the genomic OCH1 in a *Pichia* yeast

strain and/or the eukaryotic microorgainisms (e.g., Pichia yeasts) in the invention of Gerngross would constitute such a kit.

Accordingly, the teachings of Gerngross meet every limitation of the instant claims. Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 48-51, 54-57, 60-63, 69-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martinet et al. (Biotechnology Letters 20:1171-1177, 1998; IDS) in view of JP 8336387 (12/24/96; IDS).

With respect to the elected species of a combination of vectors of claims 35 and 47, Martinet et al. teaches the preparation of plasmids for expression of *T. reesei* α-1,2-mannosidase or a chimeric *S. cerevisiae/ T. reesei* α-1,2-mannosidase (a fusion of the catalytic domain of *T. reesei* α-1,2-mannosidase to the ER retention signal of *S. cerevisiae* MNS1) in *Pichia pastoris* strains GSIV-HAs and GSIVNAf1s derived from the parental strain GS115 (see Materials and Methods, particularly sections "Strains and culture conditions" and "Construction of plasmids for expression of *T. reesei* α-1,2-mannosidase in *P. patoris*"). Martinet et al. further teaches that in all expression plasmids are derived from the pPICZB vector, and the *T. reesei* α-1,2-mannosidase gene was under transcriptional control of the AOX1 promoter (page 1172, col. 2, first full paragraph). Martinet et al. also discloses that co-expression of heterologous *T. reesei* α-1,2-mannosidase in GSIVNAf1s resulting in partial trimming of the large influenza neuramidase (NA) N-glycans (>Man14GlcNac2) (see section "In vivo trimming of N-glycans by heterologous *T. reesei* α-1,2-mannosidase", and Figures 2A, 3). The co-expression of the chimeric MNS1/*T. reesei* α-1,2-mannosidase in GSIV-HAs resulted in the formation of both trimmed and hyperglycosylation glycan products of hemagglutinin (HA) (see page 1175, col. 2 and Fig. 4). Additionally, Martinet et al. notes that hyperglycosylation can be prevented by expression the protein of interest in the mutant yeast strains *mnn9, och1* or in the temperature-sensitive strain *ngd-29*, where N-glycosylation is confined to the core oligosaccharide residues (page 1176, col. 1).

Martinet et al. does not teach to further transform the *Pichia pastoris* strain with a vector comprising a portion of the Och1 gene and a selectable marker gene to effect the

disruption of the genomic Och1 gene in the *Pichia pastoris* strain to reduce the glycosylation of a heterologous glycoprotein or producing a glycoprotein with reduced glycosylation; and a kit comprising the vectors and/or these further genetically modified *Pichia pastoris* yeasts.

However, at the effective filing date of the present application, JP 8-336387 already taught the preparation of a vector construct comprising a portion of *Pichia* OCH1 gene and a selectable marker gene for disruption of the genomic OCH1 in a *Pichia* yeast strain, including the GTS 115 (NRRL Y-15851) strain for inhibiting the elongation of sugar chains on glycoproteins for production of a glycoprotein having a sugar chain identical or similar to that of a medically useful biologically active protein (see at least the abstract in English, Fig. 9 on page 635 as well as col. 15, paragraph 0033).

Accordingly, it would have been obvious and within the scope of skill for an ordinary artisan to modify the method and compositions taught by Martinet et al. by at least further transforming *Pichia pastoris* strains GSIV-HAs and GSIVNAf1s expressing heterologous *T. reesei* α-1,2-mannosidase using a vector construct comprising a portion of the *Pichia* OCH1 gene and a selectable marker gene for disruption of the genomic OCH1 taught by JP 8336387.

An ordinary skilled artisan would have been motivated to carry out the above modification because the elimination of endogenous OCH1 in a *Pichia* yeast strain inhibits the addition of α-1,6-polymannose outer chain formation on the Asn-linked inner core oligosaccharide Man8GlcNAc2, and results in smaller and homogenous

oligosaccharides in heterologous glycoproteins or at least production of a glycoprotein having a sugar chain identical or similar to that of a medically useful biologically active protein as taught by JP 8-336387. Moreover, Martinet et al. already noted that hyperglycosylation can be prevented by expression the protein of interest in the mutant yeast strains *mnn9, och1* or in the temperature-sensitive strain *ngd-29*, where N-glycosylation is confined to the core oligosaccharide residues (page 1176, col. 1). The kits comprising the vector components for carrying out the modified methods and genetically modified *Pichia pastoris* yeast strains discussed above would also have been obvious.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Martinet et al., and JP 8-336387, coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 35, 38, 48-51, 54-57, 60-63, 69, 71-72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,803,225.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a genetically engineered methylotrophic yeast strain, a kit, a genetically engineered *Pichia* strain, and a method of producing a glycoprotein with reduced glycosylation and a method of reducing glycosylation of a heterologous protein expressed in a methylogropic yeast in the issued U.S. Patent 6,803,225 anticipate the claimed genus in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub- should the genus issue as a patent after the species of sub-genus.

Claim 48 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5, 7-26 of copending Application No. 10/713,970.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a genetically engineered methylotrophic yeast strain which produces glycoproteins comprising a mammalian-like N-glycan structure, wherein said strain expresses (1) an alpha-1,2-mannosidase or a functional part thereof, (2) an N-

acetylglucosaminyltransferase I or a functional part thereof, and (3) a beta-1,4-galactosyltransferase or a functional part thereof in the copending Application No. 10/713,970 anticipates the claimed genus (a genetically engineered strain of a methylotrophic yeast, wherein said strain is transformed with at least one of the vectors of claims 35, 41 or 47) in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub- should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 48-51 and 69-72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 83, 88, 126-135 of copending Application No. 10/185,475.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a methylotrophic yeast strain, transformed with a nucleotide coding for a GlcNAc-transferase I or a functional part thereof, and also transformed with a nucleotide coding for an alpha-1,2-mannosidase or a functional part thereof, wherein both said GlcNAc-transferase I or said functional part thereof, and said alpha-1,2-mannosidase or said functional part thereof, are expressed in said methylotrophic yeast strain; and a kit for modification of protein glycosylation in a methylotrophic yeast strain in the copending Application No. 10/185,475 anticipate the claimed genus (a genetically engineered strain of a methylotrophic yeast, wherein said strain is transformed with at

least one of the vectors of claims 35, 41 or 47; a kit comprising at least one of the vectors of claims 35, 41 or 47; a kit comprising the methylotrophic yeast strain of claim 48 or claim 50) in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub- should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN
PATENT EXAMINER